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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/155,708	04/05/1999	GWENYTH JANE FARRAR	MUR-7520	9036

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	37

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/155,708	FARRAR ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 9-17-03 .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 12-22,25-27,30-38 and 41-49 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 12-22,25-27,30-38 and 41-49 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The indicated allowability of claims 46-49, and the objection to claim 27 as set forth in the prior Office Action, are withdrawn due to the following new grounds of rejection set forth below.

Response to Arguments

Claim Rejections - 35 USC § 102

3. Claims 12-14, 16-22, 25-26, and 30-38, 42-45 remain rejected under 35 U.S.C. 102(e) as being anticipated by Sidransky et al. (see entire document), for the reasons of record set forth in the Official Action mailed 2-27-03.

4. Applicant's arguments filed 9-17-03 have been fully considered but are not persuasive. Applicants traverse the instant rejection on the grounds that Sidransky et al. does not identically disclose each and every element of Applicant's claims. In particular, Applicants argue that Sidransky et al. does not disclose, or provide a motivation to create, a replacement nucleic acid that has at least one altered wobble base. Contrary, to Applicant's assertions, as stated in the prior Office Action, Sidransky et al. describe various viral vectors that can be used to deliver nucleic acid (i.e. antisense, ribozymes, or replacement genes) to cells for gene therapy purposes (col. 15, lines 18-48). In one particular example Sidransky et al., see Table 2 (col. 20), disclose target regions of mutant p53 that comprise a single nucleotide change in the wobble position of at least one codon that is not found in the wild-type p53 sequence, wherein these target regions are used to design allele specific nucleic acid. Therefore, the invention of Sidransky et al.

contemplates the design of suppression effector that targets a mutant allele that differs from a replacement nucleic acid by at least one degenerate/ wobble site.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 12, 14, 21, 26-27, 33, 42-44, 51, 53, 55, 59, 61, 63-64, 70-71, 73, 75-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Robinson-Benion et al.

Robinson-Benion et al. describe a method for combined antisense inhibition and gene replacement. This method comprises the delivery of an antisense-resistant expression vector that was constructed by cloning a portion of human c-fos cDNA into a Moloney LTR-regulated expression vector. The cloned human c-fos cDNA comprises a deletion that removes the sequences that are complementary to an 84 base pair antisense c-fos construct. Absent evidence to the contrary, this deletion mutant of c-fos cDNA, comprises at least one alteration at a wobble/degenerate nucleotide.

Robinson-Benion et al. teach each and every aspect of the instantly claimed invention, thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 12, 25, 41-44, 51, 62-64, 70-71, 73, and 75-77 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the Official Action mailed 2-27-03.

9. Applicant's arguments file 9-17-03 have been fully considered, but they are not persuasive. Applicants traverse the instant rejection by way of canceling claims 15 and 31. However, independent claims 12, 44 and 51 still encompass wherein the suppression effector recited in the instant claims are not limited to a nucleic acid based suppression effector. As recited in the specification as filed, page 2, lines 26-31: "Generally, suppression effectors, *such as* nucleic acids -antisense or sense, ribozymes, peptide nucleic acids (PNAs), triple helix forming oligonucleotides, peptides and/ or antibodies directed to sequences in a gene, in transcripts or proteins, can be employed in the invention to achieve gene suppression." It is noted that the definition of the "suppression effector" set forth in the specification as filed, can not be considered as having a special or limiting definition, due to the breadth of the language used in the definition, particularly wherein the definition recites "*such as* nucleic acids.." It appears that the suppression effectors of the present invention encompass compounds beyond those described in the specification as filed, and those described in the claims.

As stated in the prior Office Action, the instant claims recite a suppression effector, wherein the suppression effector suppresses the expression of a mutant allele and does not inhibit the replacement nucleic acid that differs from the mutant allele by having one or more degenerate/wobble sites. To the extent that the "suppression effector" encompasses a peptide,

antibody, or other form of suppression effector, the specification as filed fails to disclose at least one embodiment wherein the suppression effector is either a peptide or antibody and wherein the peptide or antibody functions to inhibit the expression of a mutant allele and does not inhibit a replacement nucleic acid.

Moreover, due to the lack of description in the specification as filed, it is unclear how one of skill in the art would be able to predict the structures of peptides, antibodies, and/or other forms of suppression effectors, which possesses the required functionality as set forth in the instant claims. One of skill in the art would have to resort to trial and error experimentation in order to identify the full scope of compounds encompassed by the claimed invention. In light of the fact that further experimentation is required to identify the full scope of compounds that are useful in the claimed methods and kits, it is apparent that full scope of the claimed invention was not reduced to practice at the time of filing of the claimed invention. Therefore, the full scope of the claimed invention was not "ready for patenting" at the time of filing of the present invention.

10. Claims 46-49 and 65-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to ribozymes or compositions comprising ribozymes. However, the ribozymes according to the present invention that comprise nucleotides 101-137 of SEQ ID NO: 4, nucleotides 116-153 of SEQ ID NO: 14; nucleotides 112-148 of SEQ ID NO: 15; or nucleotides 107-141 of SEQ ID NO: 18 comprise DNA sequences instead of an RNA

sequence. Although, DNAzymes are known in the art, Applicant's have not provided any evidence that the ribozymes of the present invention function as DNAzymes. The ribozymes described in the specification as filed are described as hammerhead ribozymes, however the sequences set forth for Rz10, Rz20, Rz33, Rz30, Rz31 (for example, see pages 20-24), are described as DNA sequences. See Figure 3 of US Patent No. 6,326,174, which describes the conserved nucleotide structure of DNAzymes. It is noted that the DNA sequences of the ribozymes according to the present invention do not comprise all the conserved nucleotide sequences that are common to DNAzymes.

Furthermore, it is well known in the art that ribozymes require the presence of the 2'-OH hydroxyl in the ribose sugar for catalysis of RNA cleavage, see for example Figure 1, page 1146 of Takagi et al. (2002), and Burke (2002) 1st ¶, page 1118. Therefore, the specification as filed does not provide sufficient guidance and/or instruction that would allow the skilled artisan to use the ribozymes sequences of the claimed invention, which comprise a DNA sequence, without undue experimentation. This conclusion is based upon the well-established knowledge in the ribozymes art, that ribozymes are single-stranded RNA molecules, and the lack of guidance provided in the specification as filed for using DNA molecules as ribozymes.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

12. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 30, 32-37, 41-45, 52, 60-64, and 68-77 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 77-140 of copending Application No. 09/043,506. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application, drawn to therapeutic compositions for treating a genetic disease, are an obvious variant of the invention encompassed by the instantly claimed invention. The claims of the co-pending application are drawn to compositions comprising a suppression effector that binds to an untranslated region of a mature RNA encoding a mutant allele, wherein said suppression effector inhibits the expression of the mutant allele and a replacement nucleic acid that expresses a wild-type or non-disease causing allele and that is not inhibited by the suppression effector. The claims of the current application are drawn to compositions comprising a suppression effector that that suppresses the expression of a mature RNA encoding a mutant allele, and a replacement nucleic acid that encodes a wild-type or non-disease causing allele, and that differs from the mutant allele in at least one degenerate / wobble nucleotide. The

claims of the current application and those of the co-pending application differ to the extent that the compositions of the current application are generally drawn to compositions comprising a suppression effector that targets the mature RNA of a mutant allele, and wherein the replacement nucleic acid contains at least one difference at a degenerate / wobble nucleotide in comparison to the mutant allele. Similarly, the claims of the co-pending application are also drawn to compositions comprising a suppression effector that targets mature RNA of a mutant allele, however the claims are limited to the untranslated portion of a mutant allele. Additionally, the claims of the co-pending application read on compositions comprising a replacement nucleic acid that encodes a wild-type or non-diseased allele. Although, the co-pending claims do not recite that the replacement nucleic acid comprises at least one change at a degenerate/wobble site, it is well known in the art that point mutations at degenerate/wobble sites are silent mutations that generally produce nucleic acid molecules that encode wild-type proteins. Moreover, the untranslated region of a mature RNA represents a specific target region that encompassed within the broad target of a mature RNA. The various regions of a mature RNA, represents a limited and well known number of species, including for example, the 5' and 3' untranslated regions, the translation start region, the coding sequence, and the translation termination region. Therefore, claims that encompass wherein the suppression effector targets a mature RNA, inherently encompasses these various regions, and the number of regions are so limited such that each region is immediately contemplated.

Therefore, the subject matter as a whole in the instantly claimed invention, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains, over the compositions claimed in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE